Antibody-based radiopharmaceuticals for imaging and therapy

Holland, Jason P

DOI: https://doi.org/10.1002/jlcr.3636

JLCR Special Issue

Antibody-based radiopharmaceuticals for imaging and therapy

Jason P. Holland*

University of Zurich, Department of Chemistry, Winterthurerstrasse 190, CH-8057, Zurich, Switzerland

*** Correspondence:**

Prof. Dr Jason P. Holland

Tel: +41.44.63.53.990

E-mail: jason.holland@chem.uzh.ch

Editorial

The objective of this special issue was to highlight the chemical and biochemical factors that must be considered during the development of antibody-based radiopharmaceuticals for immuno-PET, immuno-SPECT and/or radioimmunotherapy (RIT). Notably, common subjects such as bioconjugation and modern site-specific labelling methods are not included since many excellent resources already exist. Rather, the emphasis is on the practicalities of working with radiolabelled antibodies with the aim of providing a brief, thought-provoking overview of the key concepts in radioimmunoconjugate design.

Current trends in the pharmaceutical industry have witnessed wide-spread growth in area of biological products. Monoclonal antibodies and antibody-drug conjugates (ADCs) constitute more than 15% of the total number of New Molecular Entities that have received US-FDA approval since 2011. The radiochemistry community has also taken advantage of the growth in biologics, and nowadays, many new radiopharmaceuticals for diagnostic imaging and targeted radionuclide therapy are built upon antibody-based scaffolds. From the outside, the production of radiolabelled antibodies can appear deceptively simple – with the antibody in hand, the main work can be distilled to a two-step process involving bioconjugation of the protein with a metal binding chelate, followed by radiolabelling and purification. Standard protocols exist for both reaction steps. However, many potential pitfalls lie in wait for those inexperience in the subtleties of handling sensitive proteins.

In their work entitled, 'Preclinical optimization of antibody-based radiopharmaceuticals for cancer imaging and radionuclide therapy…', Carter *et al*. provide a thorough account of many factors that must be incorporated into a comprehensive study design aimed at preclinical evaluation of radiolabelled antibodies. One aspect is the choice of radionuclide. Here, Aluicio Sarduy *et al*.

discuss the production and radioactive properties of several radiometals with potential use in immuno-PET. As most radiochemists know well from experience, the chemistry of the radionuclide plays a crucial role in the stability and pharmacokinetics of a radiotracer *in vivo*. My contribution, co-authored with Eszter Boros, looks at some of the chemical aspects of metal ion chelation in the synthesis of antibody-based radiotracers. Moving beyond the radiochemistry, Vivier *et al*. provide a fascinating and unique insight into the '…*in vivo* fate of radioimmunoconjugates for PET and SPECT'. High uptake and accumulation of radioactivity in organs like the liver, spleen and kidneys is sometimes attributed to instability of the radiotracer *in vivo* (for example, arising from the release of the metal ion from the chelate, antibody dimerisation or protein denaturation etc) but a more complete picture of the pharmacokinetics must also consider the natural uptake, metabolism and excretion pathways of antibodies themselves. Antibodies derived from natural selection methods are just one source of radioimmunoconjugates. Arguably a more advanced strategy to control pharmacokinetics is to 'design' new antibody-based constructs using protein engineering tools. Here, Tsai and Wu review current progress in the area of '…engineering antibodies for radionuclide delivery'. Finally, two articles review the current state of clinical research using antibody-based radiopharmaceuticals: Mark Bartholomä offers an up-to-date perspective on 'Radioimmunotherapy of solid tumours', while McKnight and Viola-Villegas consider the rise in immunoPET using ^{89}Zr-radiolabelled antibodies as companion diagnostics in clinical drug development.

My hope is that the articles in this special issue will be of value to both experienced radiochemists working with antibodies, as well as students and those new to the field of radioimmunoconjugates.